

5

What is claimed is:

1. A transgenic nonhuman mammal having a transgene comprising:  
a promoter and enhancer from the same mammary gland specific gene;  
10 a secretory DNA segment encoding a signal peptide functional in  
mammary secretory cells of the transgenic nonhuman mammal, and  
a recombinant DNA segment encoding acid .alpha.-glucosidase operably  
linked to the secretory DNA segment to form a secretory-recombinant  
DNA segment, the secretory-recombinant DNA segment being operably  
15 linked to the promoter and enhancer, and wherein the secretory DNA  
segment is an acid .alpha.-glucosidase secretory DNA segment or is from the  
same mammary-gland specific gene as the promoter and enhancer;  
wherein the transgene, in an adult form of the nonhuman mammal or a  
female descendant of the nonhuman mammal, expresses the secretory-  
20 recombinant DNA segment in the mammary secretory cells to produce  
acid .alpha.-glucosidase that is processed and secreted by the mammary  
secretory cells into milk in a recoverable amount with .alpha.-glucosidase  
catalytic activity.
2. The transgenic nonhuman mammal of claim 1, wherein the concentration  
25 of the acid .alpha.-glucosidase in the milk is at least 100 .mu.g/ml.
3. The nonhuman transgenic mammal of claim 1, wherein the secretory DNA  
segment is an acid .alpha.-glucosidase secretory DNA segment.
4. The transgenic nonhuman mammal of claim 1, wherein the human acid  
.alpha.-glucosidase is secreted into milk in a form that can be taken up by  
30 muscle cells.
5. The nonhuman transgenic mammal of claim 1, wherein the acid .alpha.-  
glucosidase is human.
6. The nonhuman transgenic mammal of claim 5, that is a mouse or rabbit.
7. The nonhuman transgenic mammal of claim 6, wherein the recombinant  
35 DNA segment is cDNA.

- 5     8. The nonhuman transgenic mammal of claim 6, wherein the recombinant DNA segment is genomic.
9. The nonhuman transgenic mammal of claim 6, wherein the recombinant DNA segment is a cDNA-genomic-DNA hybrid.
10. A method for producing acid .alpha.-glucosidase, the method comprising:  
10     recovering milk from the adult form of the transgenic nonhuman mammal of claim 1 or its female descendant, wherein said milk contains a recoverable amount of acid .alpha.-glucosidase with catalytic activity.
11. The method of claim 10, further comprising incorporating the milk into a food product.
- 15     12. The method of claim 10, further comprising purifying the acid .alpha.-glucosidase from the milk.
13. The method of claim 12, wherein the acid .alpha.-glucosidase is purified to at least 95% pure from other components of the milk.
14. The method of claim 13, further comprising mixing the acid .alpha.-  
20     glucosidase with a pharmaceutical carrier for intravenous, intradermal, intramuscular or oral administration.
15. Milk from the transgenic nonhuman mammal of claim 1, the milk comprising human acid .alpha.-glucosidase in a recoverable amount.
16. The milk of claim 15, wherein the concentration of the human acid .alpha.-  
25     glucosidase is at least 100 .mu.g/ml.
17. A composition comprising human acid .alpha.-glucosidase with catalytic activity and capacity to be taken up by muscle cells in a patient and milk of the nonhuman transgenic mammal of claim 1.
18. A pharmaceutical composition for parenteral administration to a human  
30     patient comprising human acid .alpha.-glucosidase with catalytic activity and in a therapeutically effective dosage to treat a patient suffering from Pompe's disease; and a pharmaceutical carrier, the composition being free of other human proteins present in its natural environment.
19. The pharmaceutical composition of claim 18, wherein the pharmaceutical  
35     carrier is for intravenous administration.
20. The pharmaceutical composition of claim 18, wherein the human acid .alpha.-glucosidase is purified to homogeneity.

- 5 21. A method of treating a patient with Pompe's disease, comprising:  
administering to the patient a therapeutically effective amount of human  
acid alpha glucosidase.
22. The method of claim 21, wherein the patient is administered at least 10  
mg/kg body weight per week.
- 10 23. The method of claim 21, wherein the patient is administered at least 15  
mg/kg body weight per week.
24. The method of claim 21, wherein the patient is administered at least 20  
mg/kg body weight per week.
25. The method of claim 21, wherein the patient is administered at least 30  
15 mg/kg body weight per week.
26. The method of claim 21, wherein the patient is administered at least 45  
mg/kg-60 mg/kg body weight per week.
27. The method of claim 21, wherein the patient is administered at least 60  
mg/kg body weight per week.
- 20 28. The method of claim 21, wherein the patient is administered at least 120  
mg/kg body weight per week.
29. The method of any of claims 21-28, wherein the patient is administered a  
single dosage of alpha-glucosidase per week.
30. The method of any of claims 21-28, wherein the patient is administered  
25 two dosages of alpha-glucosidase per week.
31. The method of any of claim 21-28, wherein the patient is administered  
three dosages of alpha-glucosidase per week.
32. The method of any of claims 21-31, wherein the amount is administered  
per week for a period of at least four weeks.
- 30 33. The method of any of claims 21-31, wherein the amount is administered  
per week for a period of at least 24 weeks.
34. The method of any of claim 21-33, wherein the alpha-glucosidase is  
administered intravenously.
- 35 35. The method of claim 21, wherein the alpha-glucosidase was produced in  
milk of a transgenic mammal.
36. The method of claim 21, wherein the alpha-glucosidase was produced  
from a CHO cell-line.
37. The method of claim 21, wherein the patient has infantile Pompe's disease.

- 5 38. The method of claim 21, wherein the patient survives to be at least one  
year old.
39. The method of claim 21, wherein the patient has juvenile Pompe's disease.
40. The method of claim 21, wherein the patient has adult Pompe's disease.
41. The method of claim 21, wherein the alpha-glucosidase is predominantly  
10 in a 110 kD form.
42. The method of claim 21, further comprising monitoring a level of human  
acid alpha glucosidase in the patient.
43. The method of claim 21, further comprising administering a second dosage  
of human acid alpha glucosidase if the level of alpha-glucosidase falls  
15 below a threshold value in the patient.
44. The method of claim 21, wherein the human alpha glucosidase is  
administered intravenously and the rate of administration increases during  
the period of administration.
45. The method of claim 44, wherein the rate of administration increases by at  
20 least a factor of ten during the period of administration.
46. The method of claim 44, wherein the rate of administration increases by at  
least a factor of ten within a period of five hours.
47. The method of claim 21, wherein the patient is administered a series of at  
least four dosages, each dosage at a higher strength than the previous  
25 dosage.
48. The method of claim 47, wherein the dosages are a first dosage of 0.03-3  
mg/kg/hr, a second dosage of 0.3-12 mg/kg/hr, a third dosage of 1-30  
mg/kg/hr and a fourth dosage of 2-60 mg/kg/hr.
49. The method of claim 47, wherein the dosages are a first dosage of 0.11  
30 mg/kg/hr, a second dosage of 1-4 mg/kg/hr, a third dosage of 3-10  
mg/kg/hr and a fourth dosage of 6-20 mg/kg/hr.
50. The method of claim 47, wherein the dosages are a first dosage of 0.25-4  
mg/kg/hr, a second dosage of 0.9-1.4 mg/kg/hr, a third dosage of 3.6-5.7  
mg/kg/hr and a fourth dosage of 7.2-11.3 mg/kg/hr.
- 35 51. The method of claim 23, wherein the dosages are a first dosage of 0.3  
mg/kg/hr, a second dosage of 1 mg/kg/hr, a third dosage of 4 mg/kg/hr and  
a fourth dosage of 12 mg/kg/hr

- 5 52. The method of any of claims 47-51, wherein the first, second, third and  
fourth dosages are each administered for periods of 15 min to 8 hours.
53. The method of any of claims 47-51, wherein the first, second, third and  
fourth dosages are administered for periods of 1 hr, 1hr, 0.5 hr and 3 hr  
respectively.
- 10 54. A pharmaceutical composition comprising human acid alpha . glucosidase,  
human serum albumin, and a sugar in a physiologically acceptable buffer  
in sterile form.
55. The pharmaceutical composition of claim 54 comprising human acid alpha  
glucosidase, human serum albumin, and glucose in sodium phosphate  
15 buffer.
56. A pharmaceutical composition comprising alpha glucosidase, mannitol and  
sucrose in an aqueous solution.
57. The pharmaceutical composition of claim 56, wherein the sugar comprises  
mannitol and sucrose and the concentration of mannitol is 1-3% w/w of the  
20 aqueous solution and the concentration of sucrose is 0.1 to 1 % w/w of the  
aqueous solution.
58. The pharmaceutical composition of claim 56, wherein the concentration of  
mannitol is 2% w/w and the concentration of sucrose is 0.5% w/w.
59. A lyophilized composition produced by lyophilizing a pharmaceutical  
25 composition comprising human acid glucosidase, mannitol and sucrose in  
aqueous solution.
60. A pharmaceutical composition prepared by lyophilizing a first composition  
comprising human acid alphagucosidase, mannitol, sucrose and an  
aqueous solution to produce a second composition; and reconstituting the  
30 lyophilized composition in saline to produce a third composition.
61. The pharmaceutical composition of claim 60, wherein the human acid  
alpha-glucosidase is at 5 mg/ml in both the first and third composition, the  
mannitol is at 2 mg/ml in the first composition, the sucrose is at 0.5 mg/ml in  
the first composition, and the saline used in the reconstituting step is 0.9%  
35 w/w.